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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/676,718	09/28/2000	Vadim N. Gladyshev	4239-56113	1779

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EXAMINER
RAWLINGS, STEPHEN L

ART UNIT	PAPER NUMBER
1642	

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13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/676,718	Applicant(s) GLADYSHEV ET AL.	
	Examiner Stephen L. Rawlings, Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2003 and 03 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51-53,55,60,63,64 and 66-82* is/are pending in the application.

4a) Of the above claim(s) *78 and 79* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-53,55,60,63,64,66-77 and 80-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *51-53,55,60,63,64 and 66-82* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1 1/2* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The election with traversed filed January 7, 2003 in Paper No. 12 is acknowledged and has been entered.

2. Claims 51-53, 55, 60, 63, 64, and 66-82 are pending in the application. Claims 78 and 79 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12.

3. Claims 51-53, 55, 60, 63, 64, 66-77, and 80-82 are currently subject to examination.

Election/Restrictions

4. Applicant's elections with traverse of group IV in Paper No. 10, and of group I in Paper No. 12 are acknowledged. The traversals are on the grounds that the polynucleotide sequence set forth in SEQ ID NO: 4 is contained by the polynucleotide sequence set forth in SEQ ID NO: 1. Accordingly, Applicants have asserted that the restriction is improper since it would not constitute a serious burden to search and examine the claims drawn to a method comprising measuring a nucleic acid molecule comprising SEQ ID NO: 1 or SEQ ID NO: 4, as opposed to searching and examining the claims just insofar as the claims are drawn to a method comprising measuring a nucleic acid molecule comprising SEQ ID NO: 1. Similarly, Applicants have argued that because SEQ ID NO: 3 is a subsequence of SEQ ID NO: 2, the restriction is improper. In addition, Applicants have asserted that it is improper to restrict dependent claims 78 and 79 from independent claim 51. For these reasons, Applicant has requested rejoinder of particular groups.

In reply to Applicants' request for rejoinder, because SEQ ID NO: 3 is a subsequence of SEQ ID NO: 2, and SEQ ID NO: 4 is a subsequence of SEQ ID NO: 1 and because the claim 1 is drawn to nucleic acid molecules and specifically encompass fragments of SEQ ID NO: 1 or SEQ ID NO: 2, groups I and II of Paper No. 8 are rejoined, and groups X and XI of Paper No. 8 are rejoined. For the same reason, groups IV and V of Paper No. 8 are rejoined, groups VII and VIII of Paper No. 8 are rejoined, groups XXXIII and XXXIV of Paper No. 8 are rejoined, and groups XXXVI and XXXVII of Paper No. 8 are rejoined.

Otherwise, Applicants' arguments have been carefully considered, but not found persuasive, because the search required to examine any one group of inventions is not co-extensive with the search that would be required to examine any other group and because the claims are drawn to materially different methods, which have different objectives and criteria for success, or comprise different steps. For example, although Applicants have requested rejoinder of groups XV and XVI of Paper No. 8, the inventions comprise different steps and have a different criteria for success; moreover, practicing the claimed inventions would produce different results, since detecting a polymorphism in a nucleic acid molecule comprising SEQ ID NO: 3 would not necessarily detect a polymorphism in a nucleic acid molecule comprising SEQ ID NO: 2. As another example, Applicants have requested rejoinder of groups XLV and XLVI of Paper No. 8; however, the inventions comprise materially different steps and have a different criteria for success. Although SEQ ID NO: 4 is contained in SEQ ID NO: 1, the specification teaches that the polypeptide of SEQ ID NO: 4 is a putative mature form of the polypeptide of SEQ ID NO: 1 arising from post-translation modification, and while the expression of one "isoform" of a protein may be associated with the onset or progression of cancer, another isoform may not be. The art teaches that one cannot predict whether one isoform will have the same function as another, or be expressed in the same manner as another. For example, Li, et al (Growth Factors 19: 49-59, 2001) teach that two isoforms of

VEGF-B are expressed differently; one is over-expressed in some tumor cell lines, while the other is not.

Additionally, in reply to Applicants' assertion of the impropriety of restricting claims 78 and 79 from claim 51, claims 78 and 79 were not restricted from claim 51; the groups, namely groups III and IV of Paper No. 11 in which claims 78 and 79 are included, also include claim 51. The inventions of groups III and IV are distinct from the inventions of the other groups for the reasons set forth in Paper No. 11. Therefore, excepting the rejoinders set forth in the paragraph above, the restriction requirement is deemed proper and made FINAL.

Specification

5. The disclosure is objected to because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code, which are impermissible and require deletion. See pages 6, 7, and 14, for examples.

The attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP § 608.01(p), paragraph I regarding incorporation by reference.

6. The specification is objected to because the use of numerous improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

For example, Phosphorimager™ is the registered trademark of Molecular Dynamics, Inc, but has been used inappropriately on page 12 of the current specification.

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the

appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

Claim Objections

7. Claims 51-53, 55, 60, 63, 64, 66-77, and 80-82 are objected to because the claims are drawn in the alternative to the subject matter of non-elected inventions. Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 52, 60, 66, 70, 77, and 82 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 52 recites the limitation "is reduced by at least 3-fold"; and claim 66 recites the limitation "is reduced by at least 5-fold". The disclosure on page 2 of the specification to which Applicants have referred for support does not provide a proper and sufficient antecedent basis. Accordingly, the recitation of these limitations in the present claims appears to introduce new matter and thereby violates the written description requirement set forth under 35 USC § 112, first paragraph. These issues might be resolved by amending the claims to recite the explicit language set forth in the specification.

Claim 60 recites, "wherein the cancer is selected from the group consisting of [...] head and neck cancers, and colon cancer"; and claim 82

recites, "wherein the cell of the subject is a thyroid [...] cell". While the specification discloses that Applicants measured the frequency at which the gene encoding the polypeptide of SEQ ID NO: 1 is expressed in a colon cancer EST library, or a thyroid and a parathyroid tumor EST library, the specification does not appear to disclose a method for determining if a subject is at risk for developing colon or thyroid cancer, wherein said method comprises determining if a cell of the subject, namely a colon or thyroid cell has a reduced expression of the polypeptide of SEQ ID NO: 1 relative to a control cell. Furthermore, while the specification discloses that Applicants measured the frequency of select polymorphisms in the gene encoding the polypeptide of SEQ ID NO: 1 in head and neck cancers, the specification does not appear to disclose a method for determining if a subject is at risk for developing head and neck cancers, wherein said method comprises determining if a cell of the subject has a reduced expression of the polypeptide of SEQ ID NO: 1 relative to a control cell. Accordingly, there does not appear to be proper and sufficient antecedent basis in the specification for recitation of these limitations in the claims. However, this issue might be resolved if Applicants were to point to specific disclosures that are believed to provide the necessary intrinsic, explicit, or expressive support.

Claim 70 recites the limitation "any 15 kDa selenoprotein"; however, the specification does not appear to provide proper and sufficient support for the recitation of this limitation in the claims, since it appears that the specification teaches *the* 15 kDa selenoprotein, rather than a genus of 15 kDa selenoproteins. While it thus appears that the recitation of "any 15 kDa selenoprotein" in the claims introduces new matter, this issue might be resolved if Applicants were to point to specific disclosures that are believed to provide the necessary antecedent basis.

Claim 77 recites the limitation "wherein the antibody is bound to a solid support". Antecedent basis for this limitation cannot be found in the specification; however, Applicants were to point to specific disclosures that are believed to provide the necessary support, this issue might be resolved.

10. Claims 51-53, 55, 60, 63, 64, 66-77, and 80-82 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method comprising measuring the expression of a genus of polypeptides comprising an amino acid sequence having at least 70% identity to SEQ ID NO: 1. However, the specification only provides an adequate description of the polypeptide of SEQ ID NO: 1 and fails to disclose how the polypeptide of SEQ ID NO: 1 is to be regarded as representative of the genus of polypeptides to which the claims refer. For example, the specification does not describe a correlation of particular structural and functional features, which are common to at least a substantial number of members of the genus of polypeptides to which the claims refer. Moreover, the specification fails to describe which amino acids of the polypeptide of SEQ ID NO: 1 are critical to the structure and function of the polypeptide, or which amino acids might be replaced, and by which other amino acids, so that the resultant polypeptide would be expected to retain the structure and function of the polypeptide of SEQ ID NO: 1. Additionally, the specification does not describe the detailed structure of any other human protein having at least 70% identity to SEQ ID NO: 1. Although the specification also describes the polypeptide of SEQ ID NO: 9, the specification fails to disclose how the mouse homolog of the polypeptide of SEQ ID NO: 1 is to be regarded as representative of the genus of polypeptides to which the claims refer. Accordingly, the specification fails to describe the claimed invention in such a way as to reasonably convey to the skilled artisan that the Applicants were in possession of the claimed invention at the time the application was filed, because even given the benefit of Applicants' disclosure, one skilled in the art could not instantly envision or recognize at least a

substantial number of the members of the genus of polypeptides to which the claims refer.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant

in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

Skolnick, et al (*Trends in Biotechnology* **18**: 34-39, 2000) disclose that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, *Sequence-based approaches to function prediction*). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see, in particular, the abstract and Box 2). Thus, one skilled in the art would not accept the assertion, which is based only upon an observed similarity in amino acid sequence, that a variant of the polypeptide of SEQ ID NO: 1 would function similarly to the polypeptide of SEQ ID NO: 1. Therefore, one skilled in the art would not accept the assertion, which is based only upon an observed similarity in amino acid sequence, that the level of expression of a variant of the polypeptide of SEQ ID NO: 1 would be indicative of a subject's risk for developing cancer.

As evidenced by the teachings of Skolnick, et al, the art is unpredictable. The *Guidelines* state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus.

11. Claims 51-53, 55, 60, 63, 64, 66-77, and 80-82 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The teachings of the specification cannot be extrapolated to the enablement of the claimed invention because the amount of guidance, direction, and exemplification set forth therein is insufficient to enable the skilled artisan to have a reasonable expectation of successfully using the claimed invention without need to perform additional, undue experimentation. The factors that have been considered in determining that undue experimentation would be required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The molecular diagnosis of cancer, the molecular assessment of a cancer patient's prognosis, or the molecular assessment of a subject's risk for developing cancer is a highly unpredictable art, because of the complexities of the biological systems and the many and variable mechanisms by which cancer forms and progresses. In the absence of scientific and clinical validation of the utility of a biomarker, such as the 15 kDa selenoprotein that is disclosed by Applicants, the skilled artisan could not have a reasonable expectation of successfully using the claimed invention to assess a subject's risk for developing cancer.

The teachings of Rae, et al (*International Journal of Cancer* **88**: 726-732, 2000) emphasize the need to first scientifically validate the utility of a proposed biomarker by carefully controlled studies. Rae, et al teach a highly sensitive method for determining the differential expression of genes associated with renal cell carcinoma (RCC) (abstract). A total of sixteen tumor and sixteen adjacent normal tissue samples were collected at the same time from the patients. The

tumor tissue was histologically confirmed to be clear-cell RCC; and the tumors were staged by a conventional system. Rae, et al discloses that using differential display PCR, some genes were identified that are expressed at higher levels in the tumor specimens than in the normal specimens, while other genes were expressed at lower levels in the tumor specimens. Notably, Rae, et al had planned to use as a positive control, primers that amplify a cDNA encoding DD96, a gene that had been previously reported by Kocher, et al to be up regulated in RCC. However, Rae, et al found in contrast to the results reported by Kocher, et al, no *consistent* up- or down-regulation of *DD96* was evident when using either RT-PCR or Northern analysis and conclude, "we do not believe that *DD96* up-regulation is highly associated with RCC, particularly in early progression, and does not warrant extensive further investigation in the context of this disease" (page 731, column 2). Rae, et al suggest that the results of Kocher, et al were inaccurate because their experiments were not properly controlled. In contrast to the study of Kocher, et al, Rae, et al disclose, "only those cDNAs clearly up- or down-regulated in duplicate paired RCC and normal kidney samples (Fig. 1) from 4 different patients were considered to be definitively differentially expressed" (page 728, column 1). Moreover, their results were considered accurate only when the cDNAs were successfully re-amplified and only when no expression was detected in the paired sample. As the specification does not describe the use of paired samples, in view of the teachings of Rae, et al, the skilled artisan could not have a reasonable expectation of successfully using the claimed invention without having need to first perform additional, and an undue amount of experimentation to first confirm the Applicants' discovery and scientifically validate the observed under-expression of the 15 kDa selenoprotein of SEQ ID NO: 1.

Even in instances where carefully controlled experiments establish the that a biomarker is actually expressed differently by cancer cells and matched normal cells, the determination of the presence or expression of some tumor markers has proven to be ineffective in enabling an accurate diagnosis of cancer.

Ward (*Developmental Oncology* **21**: 91-106, 1985) teaches that a number of tumor-associated markers are, in fact, diagnostically unreliable (see abstract). US Patent No. 5,536,817-A teaches that even CA-125, one of the more reliably used biomarkers known in the art, is not always effective for rendering a diagnosis of ovarian cancer (see; column 2, line 47 to column 3, line 2). Just as the art teaches not all markers can be reliably used in primary diagnosis, some markers are not likely to be used to assess a subject's risk for developing cancer. Thus, while it is clear that some types of cancer cells have an altered level of expression of the nucleic acid molecule encoding the polypeptide of SEQ ID NO: 1, this data does not guarantee that its under-expression will result in a reliable assessment of a subject's risk for developing cancer; a biomarker must be clinically validated before it can be used to assess a subject's risk for developing cancer, diagnose a cancer, or assess the prognosis a subject having a cancer.

Tockman, et al (*Cancer Research* **52**: 2711s-2718s, 1992) teach considerations necessary in bringing a cancer biomarker (intermediate endpoint marker) to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to risk assessment, diagnosis, and/or prognosis of any type of cancer. Tockman, et al teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence, and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (page 2713, column 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and link those marker results with subsequent histological confirmation of

disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate endpoint marker (page 2714, column 1). Clearly, prior to the successful application of newly described markers, these must be validated against acknowledged disease end points; and, the marker predictive value must be confirmed in prospective population trials (page 2716, column 2).

If the under-expression of the 15 kDa selenoprotein were found to be scientifically and clinically significant, regarding the guidance that Applicants' disclosure provides, it is noted that claims 51-53 and 66 recite the term "control cell"; however, the identity of the control cell is not defined in the claims. If the control cell is a thyroid cell, a cell in which the specification discloses the polypeptide to be highly expressed, even a normal cell of the subject may appear to have a reduced expression of the polypeptide of SEQ ID NO: 1. In the absence of guidance as to the nature of the appropriate control cell, the claimed invention could not be used with a reasonable expectation of success to determine if a subject has an increased risk of developing cancer without the need to first perform additional, and an undue amount of experimentation, because the skilled artisan cannot predict which cells would be suitable controls, and which would not be.

Furthermore, although Applicants disclose that the polypeptide of SEQ ID NO: 1 is expressed at a reduced level in cancer cells relative to control cells, there is no factual evidence of record that any other polypeptide to which the claims refer is associated with cancer. Skolnick, et al (cited supra) teaches that assigning functional activities for any particular protein or protein family based upon sequence homology alone is inaccurate; the fact that another polypeptide comprises an amino acid sequence that is at least 70%, or even 90% identical to the amino acid sequence set forth in SEQ ID NO: 1 cannot be construed as evidence that the other polypeptides can be used as biomarkers to assess a subject's risk for developing cancer, since Skolnick, et al teaches, even in situations where there is some confidence of a similar overall structure between

two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein.

The art also teaches that although protein may have similar functions, the skilled artisan cannot predict which of these commonly functioning proteins will be associated with the onset and progression of cancer, or how the expression of the one of these proteins will differ from another in a cancer cell relative to a normal cell. Mork, et al (*Nutrition and Cancer* **37**: 108-116, 2000) teach that the expression of different selenocysteine-containing proteins, although commonly functioning as anti-oxidants, are expressed differently in tumors. For example, Mork, et al disclose a marked reduction in the expression of selenoprotein A, a variable increase in the expression of gastrointestinal glutathione peroxidase, and no alteration in the expression of thioredoxin reductase-α or plasma glutathione peroxidase in adenomas. Furthermore, Early, et al (*American Journal of Gastroenterology* **97**: 745-748, 2002) report that there is no association between the level of expression of particular selenoproteins and the stage of colorectal adenomas and cancer. Finally, Kote-Jarai, et al (*Prostate Cancer and Prostatic Diseases* **5**: 189-192, 2002) disclose the absence of a significant association between the presence of a polymorphism in a gene encoding a selenoprotein and the risk of young onset prostate cancer.

Additionally, although Applicants disclose that the polypeptide of SEQ ID NO: 1 is expressed at a reduced level in cancer cells relative to control cells, this alone does not constitute factual evidence that the reduced expression of the polypeptide is associated with an increased risk for developing cancer. As Ward (cited supra) teaches, some markers are better suited for other purposes, such as assessing the likelihood that a cancer cell will metastasize, since some markers are associated with late stage events, rather than early stage events in the onset and progression of cancer. Again, according to the teachings of Rae, et al, it is pertinent to scientifically validate a proposed biomarker using carefully controlled experiments, in which the tumors have been staged, so as to determine if the differential display of a particular protein is associated with early

or late events in carcinogenesis. As Applicants' disclosure fails to describe the stages of the tumors that were used, one skilled in the art could not use the claimed invention with a reasonable expectation of success without the need to first perform additional, and an undue amount of experimentation to determine whether the reduced expression of the polypeptide of SEQ ID NO: 1 is a common property of very early staged cancers, which might suggest that the polypeptide can be used to assess a subject's risk for developing cancer.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 51-53, 55, 60, 63, 64, 66-77, and 80-82 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 51-53, 55, 60, 63, 64, 66-77, and 80-82 are indefinite because claim 51 recites the term "an increased risk of developing cancer". Recitation of the term renders the claims indefinite because it cannot be ascertained what increased probability or likelihood constitutes said increased risk; and moreover, it is unclear relative to what standard a subject's risk is increased. Accordingly, one skilled in the art could not determine the metes and bounds of invention.

Conclusion

14. No claims are allowed.

15. The art made of record and not relied upon is considered pertinent to applicant's disclosure. Gail teaches statistical methods that can be used to validate immunodiagnostic tests. De Plaen, et al teach the expression of 12 genes of the MAGE family. Calvo, et al teach alterations in the expression of a gene encoding a selenoprotein during progression of prostate cancer. Kumaraswamy, et al teach structure-expression relationships of the gene

encoding the 15 kDa selenoprotein. Gladyshev, et al teach contrasting patterns of expression of various genes encoding selenoproteins in cancer cells.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
March 28, 2003

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600